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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,721	10/26/2001	Naohiro Terada	5853-207	9675
30448	7590	07/11/2006		EXAMINER
AKERMAN SENTERFITT				KELLY, ROBERT M
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WEST PALM BEACH, FL 33402-3188			ART UNIT	PAPER NUMBER
			1633	

DATE MAILED: 07/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/045,721	TERADA ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 15 May 2006.  
 2a) This action is FINAL.                  2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1,3,5,6,8 and 14-20 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1,3,5,6,8 and 14-20 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|  | 6) <input type="checkbox"/> Other: _____                                    |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/15/06 has been entered.

Claims 1, 5, and 8 have been amended.

Claims 1, 3, 5, 6, 8, and 14-20 are presently pending and considered.

### ***Claim Objections***

In light of Applicant's amendments, the objections to claim 1 are withdrawn.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of Applicant's amendment and argument, the rejections of Claims 1, 3, 5-6, 8, and 14-20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn.

***Claim Rejections - 35 USC § 112 – new matter***

In light of Applicant's amendments, the rejections of Claims 1, 3, 5-6, 8, and 14-20 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons necessitated by amendment, are withdrawn; however:

Claims 1, 3, 5, 6, 8, and 14-18 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1, from which all the other pending claims are dependent, and therefore encompass, encompasses culturing the ES cells for at least about 5 days in the absence of a test substance, under any conditions.

Applicant only broadly avers that support for this amendment is present in the specification, without further explanation of how the originally-filed specification and claims provide support for such a broad limitation.

The Examiner has reviewed the specification, and found that no explicit support for such a limitation exists, e.g., pp. 1-2, which provide the most explicit support for the claims, does not teach culturing prior to addition of test substances for any specific time period.

Hence, the specification provides no explicit support the limitation. However, page 16 of the specification (paragraph 2 and FIGURE 2), uses implicit disclosure of a specific experiment to show that EB bodies may differentiated from mouse ES cells, and are found attached to collagen coated culture plates, upon such differentiation of ES cells in culture. Further,

Applicant's culturing for 5 days required the culturing of cells under conditions that promote ES cell differentiation into embryoid bodies (Id.). Moreover, Applicant's equivalent to test substances were subsequently added (Id.).

Therefore, the Artisan could not determine that Applicant was in possession of a generic method to identify drug candidates for promoting tissue-specific differentiation of an ES cell, and would further determine Applicant's disclosure to indicate that embryoid bodies could be further differentiated, not ES cells.

*Response to Argument – new matter*

Applicant's argument 5/15/06 has been fully considered but is not found persuasive.

Applicant only broadly avers that no new matter has been introduced (p. 7, paragraph 2).

Such is not persuasive. Broad aversion does not supplant the need for evidence.

Therefore, the new matter rejection is newly applied.

*Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of Applicant's amendments, the rejections of Claims 1, 3, 5-6, 8, and 14-20 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record, are withdrawn; however:

Claims 1, 3, 5-6, 8, and 14-20 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claims are drawn to identifying compounds that cause ES cells to differentiate into specific tissues, however, the cells are cultured for at least about 5 days prior to adding the test substances.

The specification only provides a teaching that such culturing is to form EB bodies, which are differentiated from ES cells (e.g., p. 15 and FIGURE 2). Hence, the Artisan would not reasonably predict this method to identify compounds that cause ES cells to differentiate, but instead to identify compounds that cause EBs to differentiate into tissue-specific cell types.

Hence, the Artisan would have to experiment to determine if any specific obtained compound can actually cause differentiation of an ES cell into a specific cell type.

Such experimentation is considered undue amounting to inventing Applicant's screen for Applicant.

#### *Response to Argument – Enablement*

Applicant's argument of 5/15/06 has been fully considered but is not found persuasive.

Applicant argues that the claims are not directed to whether a test substance induces differentiation to a specific cell type, but only whether it induces differentiation (p. 8, paragraph 2).

Such is not persuasive. Applicant's preamble teaches "promoting tissue-specific differentiation" and not a generic differentiation. Further, the step of analyzing requires analysis for increased "tissue-specific gene expression". How could it possibly be anything other than a specific tissue to which it will differentiate? Lastly, the best possible support for Applicant's

culturing for 7-18 days in the presence of the test substance is for specific tissue types (pp. 9-10, paragraph bridging). Hence, the Artisan would not understand these claims to be methods to identify generic differentiation agents.

***Claim Rejections – 35 USC § 103 – Liu/Keller***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, 8 and 14-19 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO document No. WO/10535 to Liu and Leahy, et al. (1999) J. Exp. Zoo., 284: 67-81.

Claims 1, 3, 5, and 14-19 encompass a method to identify a drug candidate for promoting tissue-specific differentiation of an embryonic stem cell, comprising providing a library of at least 2 test substances, culturing the ES cells in at least 2 cultures for at least about 5 days in the absence of a test substance, contacting the cultures, separately, with either the first or second test substance, culturing for 4-18 additional days, and analyzing for increased tissue-specific gene expression. Claims 3 and 5 require the ES cells to be mammalian. Claim 8 requires one of the culturing steps to be at about 37 deg. C, in a carbon-dioxide containing incubator. Claims 14, 16, 17, 18, and 19 requiring the analyzing step to comprise isolating mRNA from the cultures, which is either isolating total RNA from the cultures or further requiring PCR to make cDNAs, using PCR, the mRNA is immobilized on a substrate, or the substrate is contacted with a probe which hybridizes to tissue-specific mRNA.

Although Liu does not define the steps contemplated by Applicant in the same manner as Applicant defines these steps, Liu obviates many of the limitations. Specifically, Liu discloses “methods to identify a therapeutic agent that modulates the expression of at least one stem cell gene associated with the differentiation … of stem cells” (Liu, ABSTRACT). Such stem cells include ES cells (e.g., p. 6, paragraph 3). Liu teaches the identification of stem cell genes that are differentially expressed at various stages of differentiation by preparing gene expression profiles before and after differentiation (Id., p. 5, lines 1-6). This encompasses defining those genes that are expressed in a tissue-specific manner, as well as those genes that are down-regulated in a tissue-specific manner, as well as those genes that are up-regulated in a tissue specific manner, and therefore, defines the markers that would be analyzed for increased specific gene expression. Further, Liu teaches comparison of the gene expression profiles with that of a stem cell population treated with a substance, to identify substances that modulate the expression of these genes, and therefore, would be associated with stem cell differentiation (Id., p. 5, lines 7-18; EXAMPLES 2-3). Moreover, Liu obviates the limitation of culturing the cells after contacting the cells with the substance, as one of ordinary skill in the art at the time of the invention would have known that time is needed to allow differentiation of the cells and changes in expression to take place, and hence, 7-18 days would be obtained depending on the specific lineage. Liu also teaches the aspects of mRNA isolation (p. 20), total cellular RNA isolation (p. 20), reverse transcription (p. 20), PCR amplification (pp. 23-24), immobilized mRNA (EXAMPLE 4), and probing for mRNA (EXAMPLE 4).

However, Liu does not teach or make obvious the prior step of culturing the cells for 5 days in the absence of a test substance or the use of mouse R1 ES cells.

On the other hand, Leahy teaches embryoid bodies can made of ES cells, which differentiate into various cells of the postimplantation embryo by culturing under specific conditions for 5 days and up (p. 70). Moreover, Leahy teaches the addition of exogenous factors to increase differentiation of these embryoid bodies into specific lineages prior to screening for markers for differentiation of these cells into specific lineages (p. 80). Also, Leahy teaches that mouse R1 cells may be used (e.g., p. 68, col. 2, paragraph 2). Lastly, it is noted that Leahy teaches the days in suspension culture to differentiate the cells into other lineages, including up to 10 days, along with various markers which are expressed.

Hence, at the time of invention, it would have been obvious to modify the methods of Liu by using the methods of Leahy to make embryoid bodies, which are then screened for factors causing further differentiation of such cells to specific cell type. The Artisan would have been motivated to do so, as Liu had taught the screening method applicable to the cells, and Leahy had demonstrated the ability to make EB cells which can then form the various lineages. Moreover, the Artisan would have had a reasonable expectation of success, as Liu had taught the screening methods, and Leahy had demonstrated the ability to make the EB bodies and differentiate the ES cells to various types of cells.

#### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, 5, 6, 8, and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO document No. WO/10535 to Liu and Leahy, et al. (1999) J. Exp. Zoo., 284: 67-81, as applied to claim 1 above, and further in view of US Pat No 5,874,301 to Keller, et al.

With regard to claim 1, the rejection is similarly obvious over Liu and Keller, as shown above. However, Liu and Leahy do not teach or make obvious the use of human ES cells, or the use of carbon-dioxide-containing environments for culturing at 37 deg. C. Further these rejections are also applied to all claims as Applicant may argue that the simple combination of Liu and Keller does not teach culturing for 7-18 days, and hence, Keller is also used to teach that the specific differentiation to hepatocytes is obvious for 14 days.

On the other hand, Keller teaches isolated embryonic cell populations (TITLE), including ES cells (e.g., col. 5, paragraphs 5-6; col. 2, lines 5-8), which cells may be cultured prior to differentiation (e.g., col. 7, paragraph 1), which cells may be then used in differentiation experiments to derive various differentiated cell types (EXAMPLES). One such cell is the hepatocyte, which required culturing under appropriate conditions (i.e., differentiation conditions) for at least about 14 days (e.g., col. 20, paragraph 4). Keller also teaches mouse embryonic stem cells (EXAMPLE 1). Such cells may also be derived from, *inter alia*, humans (col. 6, paragraph 2). Further, culturing conditions include 37 deg C and carbon-dioxide-containing environments (e.g., col. 10, paragraph 1; EXAMPLE 1).

Hence, at the time of invention, it would have been obvious to modify the methods of Liu/Leahy with the culturing conditions and cells of Keller

***Claim Rejections – 35 USC § 103***

In light of the amendments, the rejection of Claim 20 under 35 U.S.C. 103(a) as being unpatentable over Liu/Leahy or Liu/Leahy/Keller as applied to claim 1, above, and further in view of U.S. Patent No. 5,143,854 to Pirrung.

As shown above, claim 1 is obviated by Liu/Leahy or Liu/Leahy/Keller, however none of the references teach or suggest the use of gene chip technology.

On the other hand, Pirrung teaches the use of such gene chip technology for the analysis of arrays of peptides for activity (ABSTRACT). Specifically, Pirrung teaches such technology is useful for, e.g., “[s]creening large numbers of polymers for biological activity” (e.g., col. 3, lines 39-41).

Moreover, one of ordinary skill in the art at the time of invention by Applicant would have found it obvious to modify the teachings of either Liu/Leahy or Liu/Leahy/Keller by the use of gene technology as taught by Pirrung. The Artisan would have been motivated to do so because Pirrung allows for the controlled synthesis of a variety of polymers in a small space, which is particularly suited to the screening system described (ABSTRACT). Also, because both the references teach the various steps, and Pirrung has shown the gene chip technology successful, there exists a reasonable expectation of success.

***Conclusion***

No claim is allowed.

Art Unit: 1633

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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